Case No. 15-1413

United States Court of Appeals for the Federal Circuit

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Appellant,

v.

ARIOSA DIAGNOSTICS, INC.

Appellee.

ON APPEAL FROM THE UNITED STATES PATENT AND TRADEMARK OFFICE, PATENT TRIAL AND APPEAL BOARD, CASE NO. IPR2013-00308

RESPONSIVE BRIEF OF APPELLEE ARIOSA DIAGNOSTICS, INC. [CORRECTED]

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August 20, 2015

CERTIFICATE OF INTEREST

Counsel for Appellee Ariosa Diagnostics, Inc. certifies as follows:

1. The full name of every party or amicus represented by us is:

   Ariosa Diagnostics, Inc.

2. The name of the real party in interest represented by us is:

   Ariosa Diagnostics, Inc.

3. All parent corporations and any public companies that own 10 percent or more of the stock of the parties represented by us are:

   Ariosa Diagnostics, Inc. is a wholly-owned subsidiary of Roche Molecular Systems, Inc., which is a wholly-owned subsidiary of Roche Holdings, Inc. and an indirect subsidiary of Roche Holding Ltd. Novartis AG, a publicly held company, owns more than 10% of the voting shares of Roche Holding Ltd. Novartis AG has no representation on Roche Holding Ltd.'s board of directors and does not in any way control Roche Holding Ltd. or any of its subsidiaries.

4. The names of all law firms and the partners or associates that appeared for the party now represented by us in the trial court or agency or are expected to appear in this Court are:

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Dated: August 20, 2015 /s/ *David I. Gindler*

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STATEMENT OF RELATED CASES

This case is related to Case No. 3:12-cv-05501 in the United States District Court for the Northern District of California, which involves Appellant Board of Trustees of the Leland Stanford Junior University ("Stanford") and Appellee Ariosa Diagnostics, Inc. ("Ariosa"). It also involves Verinata Health, Inc. ("Verinata"), which is the exclusive licensee of the patent involved in this appeal, U.S. Patent No. 8,296,076 (the "'076 Patent"), and a wholly-owned subsidiary of Illumina, Inc. ("Illumina"). There are two patents involved in the above-mentioned case: the '076 Patent and U.S. Patent No. 8,318,430 ("the '430 Patent"). The above-mentioned case has been consolidated with two other cases: *Illumina, Inc. v. Ariosa Diagnostics, Inc.*, 14-cv-01921 (N.D. Cal. filed April 24, 2014) and *Illumina, Inc. v. Ariosa Diagnostics, Inc.*, 3:15-cv-02216 (N.D. Cal. filed May 18, 2015). The consolidated litigation is stayed pending this appeal.

The '430 Patent was involved in two *Inter Partes* Review ("IPR") proceedings: IPR2013-00276 and IPR2013-00277. Ariosa has appealed the Final Written Decisions in those proceedings. *Ariosa Diagnostics v. Verinata Health, Inc.*, 2015-1226 (Fed. Cir. filed December 29, 2014); *Ariosa Diagnostics v. Verinata Health, Inc.*, 2015-1215 (Fed. Cir. filed January 6, 2015). Illumina has also appealed the district court's denial of its motion to dismiss in Case No. 14-cv-01921. *Illumina, Inc. v. Ariosa Diagnostics, Inc.*, No. 2014-1815 (Fed. Cir. filed

September 15, 2014). On June 23, 2015, this Court issued an order vacating that appeal and remanding to the district court.

PRELIMINARY STATEMENT

Stanford appeals the Final Written Decision on IPR that the claims of the '076 Patent are invalid as either anticipated under 35 U.S.C. § 102(e) or obvious under 35 U.S.C. § 103. Stanford's arguments on appeal turn on the construction of a single phrase—"sequencing predefined subsequences"—recited in the patent's only disputed independent claim. Stanford contends that the Patent Trial and Appeals Board (the "Board") construed the phrase too broadly and erred in finding the claims invalid under that construction. But Stanford's appeal is fatally flawed. Although the Board's construction was entirely correct, it is also irrelevant: the Board determined, as a finding of fact, that the claims are invalid even under the erroneous construction advocated by Stanford. Moreover, the Board supported its factual findings with substantial evidence, and pursuant to controlling Supreme Court precedent, its decision is entitled to broad deference.

Stanford's high burden in this appeal must be considered in light of the unusual situation (of Stanford's own creation) in which this patent issued. As a threshold matter, the disputed claim term, "sequencing predefined subsequences," is not found anywhere in the patent's specification. Stanford now attempts to define it as limited to a single so-called "targeted sequencing" embodiment.

However, the language of the independent claim that incorporates this term—the starting point for any claim construction—plainly covers additional embodiments. Moreover, nothing in the specification amounts to a clear disclaimer or disavowal of patent scope.

Furthermore, the absence of any reference to "sequencing predefined subsequences" in the specification underscores that the inventors never contemplated what Stanford now contends the claims are limited to covering. Stanford coined the new term in what appears to be a deliberate, but misplaced, attempt to cover the commercially successful test offered by Ariosa. However, that test, and the claim language that Stanford mistakenly used in an attempt to copy it, bears little resemblance to any embodiment described in the patent. Stanford filed the underlying patent application on an expedited basis immediately after Ariosa scientists published an article describing certain aspects of what Stanford believed to be a competing test. Then, in collaboration with its exclusive licensee, Verinata, Stanford brought suit in district court accusing Ariosa of infringing the patent just two days after it issued. Stanford's arguments here and in the related district court litigation are not directed to what the inventors of the '076 Patent actually invented; they are attorney argument that is part of a multi-front campaign to run Ariosa out of business through patent litigation.

Setting aside the lack of merit to Stanford's arguments, it is estopped from making them because of the contradictory claim construction position it successfully advocated in the pending district court litigation. Before the district court, when its interests lied in trying to prove infringement, Stanford argued—*successfully*—that this claim term is not limited to any specific type of sequencing (and, in particular, not limited to "targeted sequencing"). But Stanford's interests changed when it came to responding in the IPR proceeding. Now seeking to avoid prior art, Stanford advocates a broadest reasonable interpretation of the term "sequencing predefined subsequences" that is actually *narrower* than the *Phillips* construction it successfully advocated in the district court. Specifically, Stanford argues that the phrase must be limited to the concept of "targeted sequencing"—yet another term found nowhere in the specification—in an effort to exclude random shotgun sequencing from the '076 Patent claims. This is the very construction that Stanford persuaded the district court to reject. Stanford's newly developed and impermissibly narrow construction is at odds with the claim language and the specification, and Stanford is judicially estopped from advocating this position.

Yet this claim construction dispute is much ado about nothing. Invalidation of the '076 Patent claims is not dependent upon an interpretation of the claims that excludes random sequencing. Rather, the Board found the '076 Patent claims to be

invalid *even under Stanford's flawed construction*. This Court should give deference to the Board's factual finding that, even under Stanford's "targeted sequencing" construction, the '076 Patent claims are anticipated and rendered obvious. Specifically, the Board found that U.S. Patent Application No. 2009/0029377 (the "Lo" reference, JA001000) discloses the "sequencing predefined subsequences" element of the claims at issue in this appeal—even if that element were limited to "targeted sequencing" as advocated by Stanford. The Board based its finding on the plain language of Lo, as well as the opinion of Ariosa's expert, Dr. Cynthia Morton, who testified that a person of skill in the art would understand Lo to disclose targeted sequencing techniques. The Board's conclusion was reasonable and based on substantial evidence, and Stanford has not identified any legitimate ground to find error. The Board's invalidity decision should be affirmed.

STATEMENT OF THE CASE

I. Technology Background

A. Deoxyribonucleic Acid ("DNA")

The '076 Patent claims are directed to prenatal genetic diagnosis of a fetal aneuploidy using methods for sequencing and analyzing fetal DNA circulating in a pregnant woman's blood (referred to as "cell-free" DNA). DNA is a nucleic acid molecule that is double-stranded in the shape of a helix. *See Ass'n for Molecular*

Pathology v. U.S.P.T.O., 689 F.3d 1303, 1310-11 (Fed. Cir. 2012), *aff'd in part, rev'd in part sub nom.* 133 S. Ct. 2107 (2013) ("*Myriad*"). DNA stores the genetic information of an organism, and is composed of individual building blocks called "nucleotides." *Id.* Each nucleotide contains one of four bases: adenine (A), cytosine (C), guanine (G), or thymine (T). The linear order of these bases in the nucleic acid chain is referred to as the DNA's "sequence," which forms the basis for the genetic code. *See id.* Because of complementary chemistry, each nucleotide base binds specifically to a particular nucleotide base on the opposite strand of the double helix: A binds specifically to T, and C binds specifically to G. *Id.* Identifying the order of the bases on one strand therefore *de facto* identifies the sequence of the opposite, or "complementary," strand. As discussed below, modern techniques for determining the linear order of nucleotides in DNA take advantage of this base-pairing specificity.

B. Chromosomes And Fetal Aneuploidy

DNA is packaged into discrete structures called chromosomes. *Myriad*, 689 F.3d at 1313. Each chromosome includes a unique combination of genes and sequence information. JA001190 at ¶ 7. A normal human has 23 pairs of chromosomes, which are designated with a number between 1 and 22 (for the autosomes) or with an X or Y (for sex chromosomes). *Myriad*, 689 F.3d at 1313. In a genetically normal individual, one chromosome in each pair is inherited from the

mother, while the other is inherited from the father. This normal chromosome distribution is referred to as "diploid" or "euploid." Sometimes, however, a fetal aneuploidy may occur, which is a disorder in which the fetus has an abnormal number of chromosomes instead of the normal 23 pairs. JA004520. The most common fetal aneuploidies are referred to as "trisomies" and involve an extra copy of a particular chromosome: Down syndrome (a trisomy of chromosome 21), Edwards syndrome (a trisomy of chromosome 18), and Patau syndrome (a trisomy of chromosome 13). *Id.*

Well before the filing of the '076 Patent, it was discovered that significant amounts of cell-free fetal DNA circulates in the mother's bloodstream. JA001198-99 at ¶¶ 27-28; JA001363 at ¶ 27. This means that cell-free fetal DNA from a trisomic chromosome will be overrepresented in a maternal blood sample as compared to cell-free fetal DNA from a diploid chromosome. JA001365 at ¶ 30. Knowledge of these natural phenomena has led to the development of non-invasive prenatal tests for fetal aneuploidy. These non-invasive tests have the advantage of avoiding the risks and inconveniences associated with subjecting a pregnant woman to invasive tests such as amniocentesis. JA001198-99 at ¶¶ 27-28.

C. Sequencing

Certain methods to detect an over-representation of a particular chromosome in cell-free DNA drawn from a maternal blood sample use a technology called

"sequencing." "Sequencing" refers to any method that determines the linear order of bases in DNA. JA001190 at ¶ 8; JA001361 at ¶ 24. When the '076 Patent was filed, a variety of sequencing techniques were known to persons skilled in the art. JA001190-97 at ¶¶ 8-23; JA001362-67 at ¶¶ 26-32. Though they vary in protocol, all of these sequencing techniques involve performing biochemical reactions on DNA and then analyzing the reaction products to determine the order of bases. *Id.*

The "sequence" data generated by a sequencing reaction can be analyzed, for example, to quantitate the amounts of particular sequences in a sample. JA001190 at ¶ 9; JA001197-98 at ¶ 24; JA001363-67 at ¶¶ 27-33. This can be done in various ways, including what Stanford refers to as "random" and "targeted" sequencing.

1. Random Sequencing

The technique that Stanford refers to as "random" sequencing at issue in this appeal is also known as "shotgun sequencing." Opening Brief of Appellant ("Brief") at 7, fn. 1. Shotgun sequencing was developed as a fast and efficient method for determining the sequences of large pieces of DNA in a sample. JA001190-93 at ¶¶ 7-15; JA001361-64 at ¶¶ 25-29. In random sequencing, DNA fragments from a sample are sequenced to create products that the '076 Patent refers to as "sequence tags." JA001193-95 at ¶¶ 15-18; JA001351-55 at ¶¶ 4-8. The '076 Patent defines a "sequence tag" as "a DNA sequence of sufficient length

that it may be assigned specifically to one of chromosomes 1-22, X, or Y." JA000071 at 8:57-59.

The "sequence tags" to which the '076 Patent refers are of unknown location in the genome unless and until they are aligned to a reference sequence and assigned to a location based on alignment with that reference sequence. JA001193-95 at ¶¶ 15-18; JA001372-73 at ¶ 44. Once they are assigned, the sequence tags can be analyzed and the data obtained from them can reveal information about the sample. JA001193-95 at ¶¶ 16-19; JA001372-73 at ¶ 44-46**.** For example, sequence tags assigned to certain predefined or predetermined regions of a chromosome can be analyzed by informatic means to determine quantitative information. JA001193-95 at ¶¶ 15-19; JA001365 at ¶ 30; JA001376 at ¶ 33. This involves, among other things, first aligning the sequence tags to a reference genome to determine their origin, assigning them to predefined portions of the genome or chromosome sequence that are of interest, then selecting and quantitating those that align to the predefined sequences using informatic techniques. *Id.*; JA000069 at 3:45-48. That quantitative information can then be used to determine, for example, whether a certain chromosome is overrepresented as compared to another in the sample. JA001363 at ¶ 27.

2. Targeted Sequencing

The term "targeted sequencing" is not used in the '076 Patent specification. Stanford has defined "targeted sequencing" as a sequencing approach that utilizes a pre-selection step to select, or "target," the DNA to be sequenced. Brief at 7. According to Stanford, the pre-selection step ensures that only certain predefined sequences are molecularly sequenced. "In other words," Stanford contends, "the pre-selection step is a physical selection step that excludes non-selected sequences from being molecularly sequenced." *Id.*

To support that definition, Stanford points to an example in the '076 Patent specification that describes "sequencing by array" or "sequencing by capture." Brief at 9 (citing JA000074 at 13:65-14:1). In sequencing by array, a subset of randomly generated DNA fragments is captured by what are known as DNA "probes," which have known sequences complementary to the fragments being captured. JA001192 at ¶ 13; JA001196-98 at 21-24; JA001365-67 at ¶¶ 31-33. These probes are attached to a solid substrate (the "array"). JA001197 at ¶ 22. Some or all of the randomly generated DNA fragments of the sample may be fluorescently labeled, and fragments complementary to the probes of known sequence on the array are captured by hybridization and visualized by the fluorescent label. *Id*.

Sequencing by array differs from shotgun sequencing in that it does not involve the generation of "sequence tags," and there is no need to "align" or "assign" any sequence tag data back to a reference genome. JA001191-93 at ¶¶ 11-14; JA001197-98 at 24; JA001365 at ¶ 31; JA001369 at ¶ 38; JA002041 at 45:13-24; JA002048 at 52:12-23. This is because the probes on the array correspond directly and uniquely to sequence locations that were known *a priori*. JA001191-93 at ¶ 14; JA001197-98 at ¶ 24; JA001365 at ¶ 38. The binding of a fragment to a probe provides the same information as would the alignment and assignment of sequence tags to a reference genome. This is because binding to the array demonstrates the presence of the complementary fragment in the sample. *Id.* Array-based hybridization thus "sequences" nucleic acids of interest by visualization of their hybridization to capture probes of a known, complementary sequence. *Id.*

Techniques were also known in the art prior to the filing of the '076 Patent that involved molecular selection of particular sequences followed by a separate sequencing step. JA001191-92 at ¶¶ 11-12, 20; JA001363-64 at ¶ 28, JA001366-67 at ¶ 32; JA001015 at ¶ 72. This is done, for example, to isolate informative cell-free DNA fragments that are known to correspond to genomic regions prior to the use of any sequencing technique. JA001195-96 at ¶ 20; JA001363-64 at ¶ 28. Unlike "sequencing by array" or "sequencing by capture," these alternative

techniques are not described in the '076 Patent specification, although they are the focus of Stanford's definition of "targeted sequencing," which involves a pre-selection step followed by a sequencing step.

Known selection techniques include enrichment by hybridization. JA001191-92 at ¶¶ 11-12; JA001195-96 at ¶ 20; JA001363-64 at ¶ 28; JA001366-67 at ¶ 32; JA001015 at ¶ 72. This involves, for example, first applying the cell-free DNA in a sample to an array containing capture probes, which bind to and isolate fragments containing predefined sequences of interest. JA001195-96 at ¶ 20; JA001015 at ¶ 72. The captured fragments could then be removed from the array and sequenced by any technique that would provide information sufficient to quantitate or analyze them. *Id.* This could be done by either a random or a targeted sequencing method, as long as the method provided the requisite quantitative data. *Id.*

II. The '076 Patent

The '076 Patent is directed to methods of testing for abnormal distribution of a chromosome in a maternal sample containing both maternal and fetal DNA. Claim 1 of the '076 Patent is the only independent claim challenged in this appeal.

A. Prosecution History

The '076 Patent issued from U.S. Patent Application No. 13/452,083 (the "'083 Application"), which was filed on April 20, 2012, two months after the

publication of a research article by Ariosa scientists about prenatal diagnostic testing. The '083 Application was prosecuted under Track One with prioritized examination according to 37 C.F.R. § 1.102(e)(1). JA004509. In less than three months, on July 12, 2012, all claims were allowed in the first office action. JA004510-17. The patent was issued within six months of its filing, on October 3, 2012.

The '083 Application disclosed approximately 1000 references. JA000041-50. Some highly relevant prior art references, such as the anticipating Lo reference at issue in this case, were among them. JA000043. The patent examiner did not mention the Lo reference in his reasons for allowance. JA004510-17. Instead, the examiner cited only three references that have little relevance to the field of noninvasive prenatal screening for chromosomal abnormalities. *Id*.; see JA001202 at ¶ 33. Specifically, the references dealt with the suppression of proto-oncogenes using RNA interference; detection of protein and nucleic acid biomarkers associated with diseases including inflammatory disease; and detection of newborn phenotypic traits including sudden infant death syndrome, cardiomyopathy, cognitive ability and lactose tolerance or intolerance. *Id*.

B. The ’076 Patent Disclosure

1. The Disclosure And Examples Of The Specification Almost Exclusively Teach Random Shotgun Sequencing

The Abstract of the ’076 Patent states that “[d]isclosed is a method . . . using direct shotgun sequencing . . . .” Consistent with that description, almost the entire patent specification, including the preferred embodiment, describes random “shotgun sequencing.” *See, e.g.*, JA000071 at 8:31-32 (titling section disclosing “shotgun sequencing” as “Detailed Description of the Preferred Embodiment”); *e.g.*, JA000073 at 11:46-54 (disclosing “mapping shotgun sequence information”); JA000074 at 13:3-10 (describing the utility of “shotgun sequencing” in the invention); JA000074-77 at 14:56-19:36 (disclosing entire subsection of preferred embodiment as “Shotgun Sequencing of Cell-Free Plasma DNA”). In addition, all examples in the “Examples” section of the ’076 Patent specification “describe the direct sequencing of cell-free DNA from plasma of pregnant women with high throughput shotgun sequencing technology . . . .” *See* JA000077 at 20:30-32; *see also* JA000077-78 at 20:30-29:59.

2. Only A Limited Disclosure In The Specification Describes What Stanford Refers To As “Targeted Sequencing”

The ’076 Patent also discloses that “[a]nother method for increasing sensitivity to fetal DNA is to focus on certain regions within the human genome,” such as by using “sequencing by array, or capture beads[.]” JA000074 at 13:53-54,

13:65-67. This is the disclosure to which Stanford (at 8) refers as the "targeted sequencing" embodiment. Notably, however, there are no *exemplified* embodiments of so-called "targeted sequencing" in the '076 Patent.[1]

The specification explains that this method is "*in one aspect* contrary to conventional massively parallel sequencing methodologies[.]" *Id.* at 14:22-25 (emphasis added). Specifically, "[t]his alternative method selectively ignores certain sequence information by using a sequencing method which selectively captures sample molecules containing certain predefined sequences." *Id*. at 14:25-29. The specification further indicates that "[o]ne may also use the sequencing steps exactly as exemplified, but in mapping the sequence fragments obtained, give greater weight to sequences which map to areas known to be more reliable in their coverage, such as exons." *Id*. at 14:29-33. Importantly, this alternative method does not specify any particular type of sequencing, instead indicating that "[o]therwise, the method proceeds as described below," *Id*. 14:33, following which is a detailed description of "Shotgun Sequencing of Cell-Free Plasma DNA," *id.* at 14:56.

[1] The entire description of this "targeted sequencing" disclosure is limited to 2½ of the 29 paragraphs in the "General Description of Method and Materials" section of the specification. *See* JA000072 at 10:57-19:36 (encompassing "General Description of Method and Materials" section); *see* JA000074 at 13:53-14:27 (containing what Stanford refers to as the "targeted sequencing" embodiment); JA000077 at 20:30-32 (describing all "examples below" as using "shotgun sequencing technology").

III. The District Court In The Related Litigation Declined To Limit "Sequencing Predefined Subsequences" To Targeted Sequencing

Stanford has asserted claims for infringement of the '076 Patent against Ariosa in a related litigation before the United States District Court for the Northern District of California, Case No. 11-cv-05501. During claim construction in that case, Stanford *successfully* argued against limiting the term "sequencing predefined sequences" to "targeted sequencing" embodiments. *See* JA002161-63; JA004527-29. In that litigation, Stanford proposed that "sequencing predefined subsequences . . ." should be broadly construed as "sequencing predetermined polymorphism independent subsequences . . . ," without any limitation on the type of sequencing, and objected to Ariosa's proposal to limit the term to "determining the order of nucleotides to selectively capture sample molecules containing sequences selected *a priori*." JA004527.

Specifically, Stanford argued in the district court that "nowhere do the claims include any sort of 'selective capture' requirement[;]" and that "[t]here is no step in between step (a) and (b) requiring that the 'maternal and fetal DNA' obtained in step (a) be 'selectively captured' prior to sequencing in step (b)." JA004528. Stanford's position was made even more clear at oral argument. JA004222-29. In opposing the idea that claim 1 is limited to a "targeted approach," Stanford argued that in fact claim 1 covers the "Illumina platform," which Stanford conceded is specifically covered by claim 4 and described in column 9 of the

specification. JA004226 at 43:7-10; JA004226-28 at 43:22-45:1. Stanford described this embodiment as involving "universal primers, so that they'll just capture basically any sequence that comes." *Id.* As to the specific embodiment on which it now bases its entire argument, Stanford argued that the disclosure at "column 14 deep in the patent," which describes "selectively ignor[ing] certain sequence information," "should not be inserted into the claim when the claim language doesn't have the limitation and there's other embodiments." JA004228 at 45:8-14.

Stanford prevailed, and the district court adopted its proposed construction. The court found that "claim 1 must encompass sequencing types that would include both massively parallel sequencing and other types of sequencing." JA002162. The court reasoned that "although the specification lists several examples of how to sequence the predefined subsequences, including the selective capture of molecules, . . . this is only one of several preferred embodiments, and it cannot be a limitation of claim 1." JA002163. Indeed, the court made it clear that the "specification expressly does not limit the patent to that method of sequencing." JA002162.

IV. Summary Of Proceedings In IPR2013-00308

A. Decision To Institute

In its decision to institute IPR, the Board, like the district court, "decline[d] to limit the term 'sequencing predefined subsequences' to a particular sequencing technique." JA000183. Rather, based on the claim language and the disclosure of the specification, JA000181-83, the Board interpreted "sequencing predefined subsequences" to mean "sequencing predefined nucleic acid molecules that uniquely map to a chromosome region of interest in a reference genome." JA000183. Based on that construction, the Board found a reasonable likelihood that claims 1-5, 7-9, and 12-13 are anticipated by the Lo reference;[2] claims 10 and 11 are obvious over the Lo and Brenner combination;[3] and claim 6 is obvious over the Lo and Li combination.[4] JA000197.

B. The Board's Final Written Decision

The Board maintained its claim construction in the Final Written Decision ("Decision"). Specifically, "consistent with the Institution Decision, [the Board] decline[d] to limit 'sequencing predefined sequences' to any particular sequencing method, but construe[d] the term as encompassing sequencing methods such as random shotgun sequencing, as well as sequencing by hybridization." JA000013.

[2] U.S. Patent Pub. No. 2009/0029377, published 1/29/2009 ("Lo").

[3] U.S. Patent Pub. No. 2006/0177832, published 8/10/2006 ("Brenner").

[4] Heng Li et al., 18 GENOME RESEARCH 1851-1856 (2008) ("Li").

The Board "decline[d] to adopt [Stanford's] proffered construction of limiting 'sequencing predefined subsequences' to targeted sequencing." JA000010.

The Board considered the evidence presented by the parties, including the expert declarations and testimony, JA000010, and supported its construction primarily with reference to the patent claims and specification. The Board noted that "the term 'targeted sequencing' nowhere appears in the Specification of the '076 patent," which is consistent with a construction that is not limited by the term "targeted sequencing" as Stanford proposed. JA000010. Moreover, the Board found that claim 1 cannot be construed to exclude shotgun sequencing because "the claim language associates 'sequencing predefined subsequences' with obtaining 'sequence tags'"—a premise that the parties in this appeal do not dispute—and "[t]he Specification of the '076 patent discusses sequence tags in the context of shotgun sequencing." *Id*. (citing the '076 patent at col. 14:56-66); *see also* Brief at 26 (conceding that "the purpose of sequencing predefined subsequences is to obtain sequence tags . . .").

The Board further reasoned that its construction "encompasses the preferred embodiment of the '076 patent, whereas [Stanford's] proffered construction limiting the method of claim 1 to 'targeted' sequencing . . . would not." JA000012. Additionally, the Board held that "the doctrine of claim differentiation supports [its] construction." *Id*. As the Board noted, "[c]laim 9 depends from claim 2, which

depends from claim 1. The claim 9 limitation—that the sequencing step is limited to sequencing only the predefined sequences—further supports [the] interpretation that 'sequencing predetermined sequences' is not limited to sequencing only the predefined sequences, but encompasses sequencing sequences in addition to the predefined sequences." *Id*.

Based on that construction, the Board held that claims 1-5, 7-9, 12 and 13 are anticipated by Lo; claims 10 and 11 are obvious over the combination of Lo and Brenner; and claim 6 is obvious over the combination of Lo and Li. JA000037.

The Board further found that its invalidity decision does not actually turn on the construction of "sequencing predetermined sequences." Specifically, the Board found that to the extent that the claim is limited to preselecting sequences, the Lo reference teaches that embodiment as well:

> As taught by Lo, hybridization based techniques, such as the use of an oligonucleotide array, may be used to first sub-select for nucleic acid sequences from certain chromosomes, such as a potentially aneuploid chromosome, as well as a second chromosome not involved in the aneuploidy being tested. *Id*. Thus, although claim 1 does not specify a pre-selection step, Lo teaches a preselection step, wherein only certain subsequences of the total fraction of genomic material obtained from the maternal sample is sequenced, wherein the subsequences are selected for using a hybridization reaction, e.g., such as hybridization to a DNA array.
>
> * * *
>
> [T]o the extent that the claim requires preselecting sequences for sequencing, we do not find convincing Patent Owner's argument that paragraph 72 of Lo does not teach a pre-selection step. . . . As taught

> by Lo (¶ 72), and acknowledged in the Specification of the '076 patent (Ex. 1001, col. 4, ll. 41–44), the fetal nucleic acids present in maternal plasma are short fragments. Lo teaches the use of an oligonucleotide (i.e., a short nucleotide molecule) array to sub-select for sequences from certain chromosomes. Thus, although Lo may in fact be using the oligonucleotide array to sub-select for sequences along the entire length of a desired chromosome, the oligonucleotides that make up the array are selecting for subsequences of the chromosome, which subsequences may then be analyzed using massively parallel sequencing. Lo thus teaches sequencing of predefined subsequences of a chromosome [under Stanford's interpretation].

JA000021; JA000024-25. Accordingly, the Board found that Lo met the "sequencing predefined subsequences" even under Stanford's proposed narrow interpretation (i.e., one that requires molecular or physical pre-selection before sequencing).

SUMMARY OF THE ARGUMENT

The Board found that the disputed claims of the '076 Patent are invalid as either anticipated or obvious no matter which of the competing claim constructions of "sequencing predefined subsequences" is applied. These were findings of fact, which are entitled to deference. The Board's fact-finding was based on substantial evidence and should be affirmed.

Although the Court need not even reach the Board's claim construction (because the claims are invalid even under Stanford's construction), in the event the Court does review it, the Court should find that the Board's claim construction was proper. In its Decision, the Board held that the broadest reasonable

interpretation of "sequencing predefined subsequences" is "not limited to any particular sequencing technique, and thus encompass[es] the use of random shotgun sequencing." *See, e.g.,* JA000009. As the Board aptly noted, Stanford's proposal to exclude the use of "random shotgun sequencing" from the claims is at odds with the claim language and the specification, and was inconsistent with the only credible expert testimony offered in the proceeding. JA000009-14.

For example, independent claim 1 recites that "sequencing predefined subsequences" is performed "to obtain a plurality of sequence tags aligning to the predefined subsequences," which the Board further recognized is discussed in the specification *only* in the context of random shotgun sequencing. JA000010. Exclusion of shotgun sequencing from the scope of the claim would impermissibly render at least the "sequence tags" term meaningless. Moreover, claim 1 simply requires "sequencing" and does not specify *how* to sequence. And to the extent Stanford argues that *what* is being sequenced—predefined subsequences—dictates *how* it should be sequenced, the open-ended nature of the claim ("comprising") does not exclude sequencing other nucleic acids in addition to sequencing the predefined subsequences.

In contrast, dependent claim 9 adds a "how to" limitation and is expressly limited to "*selectively* sequencing" the predefined subsequences—and as the Board noted, Stanford has not provided any evidence to rebut the presumption that

claim 1, from which it depends, must be broader. Accordingly, based on the claim language alone, the Board recognized that limiting claim 1 in a manner that excludes shotgun sequencing would impermissibly render meaningless the "comprising" and "sequence tag" claim terms, as well as claim 9 in its entirety.

The Board also found that Stanford's construction is incompatible with the disclosure of the Specification—particularly given that Stanford seeks to exclude the patent's preferred, and only exemplified, shotgun sequencing embodiment. The Board properly found that there was no unambiguous disclaimer in the intrinsic record of this embodiment, or indeed of any sequencing methods.

Setting aside the substantive flaws in Stanford's claim construction positions, as a procedural matter Stanford is judicially estopped from advocating them. Here, Stanford impermissibly seeks a "broadest reasonable interpretation" of the term at issue that is *narrower* than the *Phillips* construction adopted by the district court, at Stanford's urging. Stanford is judicially estopped because its positions in support of this narrower construction flatly contradict the positions it took before the district court in obtaining the broader *Phillips* construction.

On the other hand, Stanford's criticism of Ariosa for purportedly changing its positions as between the district court and the Board is misplaced. Unlike Stanford, Ariosa did not advocate a construction before the Board that is narrower

than in district court. Moreover, because Ariosa did not prevail in the district court, no judicial estoppel can apply to Ariosa.

In any event, irrespective of which construction applies, the Board correctly found that the Lo reference, both alone and in combination with the Li or Brenner references, meets every limitation of the disputed claims. Stanford's sole challenge to the Board's fact-finding on invalidity is that the Board allegedly should have credited Stanford's expert's attempts to distinguish the Lo reference—even though its expert's opinions in this regard were unsupported and contradicted by the Lo disclosure itself. It is settled law that to overturn the Board's findings on invalidity, Stanford must show more than simply the existence of an alternative conclusion that could have been drawn; it must demonstrate that ***no reasonable mind*** could have accepted the Board's supporting evidence. *See, e.g., Consol. Edison Co. v. NLRB*, 305 U.S. 197, 229 (1938). At most, Stanford shows only that the Board disagreed with Stanford's conclusions, which falls far short of the requisite showing.

The patent is invalid, and the Board's Decision should be affirmed.

ARGUMENT

I. Standard Of Review

During an *inter partes* review, the Board construes disputed limitations according to their broadest reasonable interpretation consistent with the

specification. *In re Cuozzo Speed Techs., LLC*, 778 F.3d 1271, 1281 (Fed. Cir. 2015). This Court then reviews that construction according to the standard set forth in *Teva Pharmaceuticals U.S.A., Inc. v. Sandoz, Inc.*, 135 S. Ct. 831 (2015). Pursuant to *Teva*, the Court "review[s] underlying factual determinations concerning extrinsic evidence for substantial evidence and the ultimate construction of the claim de novo." *In re Cuozzo Speed Techs.*, 778 F.3d at 1282-83.

With respect to invalidity, "[a]nticipation under 35 U.S.C. § 102 is a question of fact while obviousness under § 103 is a question of law based on underlying findings of fact." *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015). Underlying those determinations, "[w]hat a prior art reference discloses is a question of fact as to which the Board's findings are entitled to deference under the 'substantial evidence' standard." *Shimano, Inc. v. Rea*, 527 F. App'x 1002, 1006 (Fed. Cir. 2013) (non-precedential) (quoting *In re ICON Health & Fitness, Inc.*, 496 F.3d 1374, 1378 (Fed. Cir. 2007); *see also Kim v. ConAgra Foods, Inc.*, 465 F.3d 1312, 1326 (Fed. Cir. 2006) (same).

"A finding is supported by substantial evidence if a reasonable mind might accept the evidence to support the finding." *In re Antor Media Corp.*, 689 F.3d 1282, 1287 (Fed. Cir. 2012) (citing *Consol. Edison*, 305 U.S. at 229). "The possibility of drawing two inconsistent conclusions from the evidence does not

prevent an administrative agency's finding from being supported by substantial evidence." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1294 (Fed. Cir. 2012) (internal quotation marks and citations omitted). Thus, the Court may not reverse the Board's decision for lack of substantial evidence—even if it would have viewed the facts differently if sitting as the tribunal of original jurisdiction—so long as competent evidence in the record supports the Board's ruling. Even "[w]here two different conclusions may be warranted based on the evidence of record, the Board's decision to favor one conclusion over the other is the type of decision that must be sustained by this court as supported by substantial evidence." *In re Bayer Aktiengesellschaft*, 488 F.3d 960, 970 (Fed. Cir. 2007).

II. The Board Correctly Construed "Sequencing Predefined Subsequences" As Not Limited To "Targeted" Sequencing Under The Broadest Reasonable Interpretation

The Board properly construed "sequencing predefined subsequences" as "sequencing predefined nucleic acid molecules that uniquely map to a chromosome region of interest in a reference genome." JA000183; *see also* JA000013 (adopting construction from Institution Decision). Neither the claim language nor the specification limit the term to any particular form of sequencing or to sequencing ***only*** the predefined subsequences.

Stanford's challenge to the Board's construction is flawed on several grounds. As a threshold matter, Stanford does not itself propose an actual claim

construction that it argues this Court should adopt in place of the Board's construction. Rather, Stanford simply urges that the Court should ***not*** adopt a construction that allows for a shotgun sequencing approach. This improper attempt to import a negative limitation into the claims is contrary to this Court's "'heavy presumption' that claim terms carry their full ordinary and customary meaning." *See, e.g., Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1323 (Fed. Cir. 2003) (rejecting construction that would import unsupported negative limitations into claims). Stanford's arguments are belied by the claim language itself and the disclosure of the specification. Stanford's proposed non-construction should be rejected and the Board's well-supported construction should be affirmed.

A. The Language Of The Claims Requires A Construction That Covers Different Types Of Sequencing

The "claim construction analysis must begin and remain centered on the claim language itself, for that is the language the patentee has chosen to particularly point[ ] out and distinctly claim[ ] the subject matter which the patentee regards as his invention." *Source Vagabond Sys. v. Hydrapak, Inc.*, 753 F.3d 1291, 1299 (Fed. Cir. 2014).

Beginning with and centering on the claim language itself, the Board construed the term "sequencing predefined subsequences" as "not limited to any particular sequencing technique, and thus encompassing the use of random shotgun

sequencing." JA000009.[5] The Board correctly reasoned that this is the only interpretation that is consistent with the language of the claim as a whole, particularly in view of the claim's additional "sequence tags" limitation and its open-ended "comprising" language. *See, e.g.,* JA000010-11. Stanford does not address this claim language—or the Board's reasoning based upon it—in its arguments on appeal. Rather, Stanford asks the Court to reverse the Board's construction based entirely on the conclusory argument that the claim language excludes random or shotgun sequencing because it describes sequencing "***only*** 'predefined' subsequences." Brief at 24 (emphasis added). Yet the word "only" does not appear in the claim and its insertion is not supported by the record. Stanford's arguments are factually and legally baseless.

1. The "Comprising" Language Of Claim 1 Expressly Permits Sequencing Other Elements In Addition To The Predefined Subsequences

The preamble of claim 1 recites that the claimed method "comprises" sequencing predefined subsequences. This language expressly allows for the sequencing of other nucleic acids along with the predefined subsequences, so long as the predefined subsequences are sequenced. *See, e.g., Mars, Inc. v. H. J. Heinz*

[5] *See also* JA000013 ("[W]e construe 'sequencing predefined subsequences' as not limited to targeted sequencing, wherein the sequences are molecularly preselected, such as by hybridization; but also as encompassing informationally predefining the subsequences, such as through the use of the predefined windows taught by the '076 patent.").

Co., 377 F.3d 1369, 1376 (Fed. Cir. 2004) ("the transitional term 'comprising,' . . . [is] open-ended."). Stanford has offered no explanation for why "comprising" in the '076 Patent claims should be interpreted in a way that is at odds with its customary open-ended meaning. The use of "comprising" directly undermines Stanford's position that claim 1 must be confined to what it calls "targeted sequencing."

2. The Board's Construction Is Required To Give Effect To The Term "Sequence Tags"

"Claims must be interpreted with an eye toward giving effect to all terms in the claim." *Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP*, 616 F.3d 1249, 1257 (Fed. Cir. 2010) (internal quotation marks and citations omitted). Stanford's proposed construction of "sequencing predefined subsequences" fails to do that. In particular, Stanford's proposal to exclude random or shotgun sequencing from the scope of the claim fails to give effect to the claim term "sequence tags," which the specification indisputably discusses only in the context of random shotgun sequencing.

Claim element 1(b), which includes the disputed phrase, recites: "*sequencing predefined subsequences* of the maternal and fetal DNA *to obtain a plurality of sequence tags* aligning to the predefined subsequences." JA000085 (emphasis added); *see also* JA000010. The Board accurately recognized that "the claim language associates 'sequencing predefined subsequences' with obtaining

'sequence tags.'" JA000010. Stanford agrees that "*the purpose* of sequencing predefined subsequences is *to obtain sequence tags* that align to the predefined subsequences that were sequenced." Brief at 26 (emphasis added, original emphasis omitted). The Board further observed—and Stanford does not dispute—that the specification only "discusses sequence tags in the context of shotgun sequencing." JA000010; JA000074 at 14:56-66; *see also* JA001372-73 at ¶ 44 (explaining that persons skilled in the art would understand "sequence tag as used in the context of the '076 patent" as "a sequence read that is produced by shotgun sequencing.").

Stanford's proposal to limit "sequencing predefined subsequences" to a method that *excludes* random sequencing would impermissibly render the term "sequence tags" meaningless. *See, e.g., Cat Tech LLC v. TubeMaster, Inc.*, 528 F.3d 871, 885 (Fed. Cir. 2008) (refusing to adopt a claim construction which would render a claim limitation meaningless); *Elekta Instrument S.A. v. O.U.R. Scientific Int'l, Inc.*, 214 F.3d 1302, 1305-07 (Fed. Cir. 2000) (same). The Board's construction is consistent with the claim language and gives effect to all of its terms. Stanford's does not.

3. Stanford Improperly Conflates What Is Being Sequenced With How It Should Be Sequenced

Stanford's claim construction illogically leaps from the claim's actual language regarding what is being sequenced (*i.e.,* the "predefined subsequences")

to the separate and unrelated question of how they should be sequenced—which Stanford argues should involve only "targeted sequencing" and should exclude random or shotgun sequencing. Stanford's proposed limitation on the sequencing method is not found in the claim language, and is actually at odds with the stated purpose for the invention that is recited in the claims. Specifically, there is no adverb or qualifier in claim 1 that specifies *how* the *sequencing* must be done or whether the sequencing must be limited to *only* the predefined subsequences, as Stanford argues in this appeal.

As evident from the language of claim 1, the purpose of the claimed invention is to "test[] for an abnormal distribution of a chromosome" in a sample by comparing the quantity of sequence tags aligning to predefined subsequences from a chromosome suspected of aneuploidy to the quantity of sequence tags aligning to predefined subsequences from a presumably normal chromosome. JA000085; *see also* JA001203-04 at ¶ 36. The purpose is not to sequence *only* predefined subsequences or to gather information that pertains exclusively to predefined subsequences—indeed, that type of restriction is not recited anywhere in the claims. To the contrary, so long as "sequence tags aligning to the predefined subsequences" are obtained—even if other regions of DNA are also sequenced—they can be used in the claimed method to test for an abnormal distribution of a chromosome. *See id*. Moreover, the claim's only recitation of "sequencing" is in

reference to the means for obtaining those "sequence tags," s*ee* JA001203-05 at ¶¶ 36-37, and, as discussed in Argument section II.A.2 above, "sequence tags" are discussed in specification solely in connection with random sequencing.

Stanford's argument (at 25) that the "sequencing predefined subsequences" language indicates a "pre-selection step," and that this somehow means that "only specific predefined sequences are actually sequenced," is entirely conclusory. Claim 1 does not refer to "pre-selection" or any form of selective sequencing, nor does it state that *only* specific sequences are sequenced. Had Stanford wished to describe "selective" sequencing as its invention in claim 1, it certainly could have done so.

Stanford's position is also illogical. Even assuming, *arguendo*, that there is a "pre-selection step" involved in claim 1, it would not follow from the claim language that *only* the predefined subsequences are then *physically* sequenced. At most, any such pre-selection would be directed to "predefining" the subsequences of interest for later analysis. Nothing in the claim indicates *how* the "predefining" must be done, and nothing in the claim prevents it from being either biochemical or information-based. For example, pre-selection of "predefined subsequences" can be accomplished informatically and random sequencing can be used to obtain the data corresponding to the pre-defined subsequences. JA002036 at 40:13-24.

Stanford also contends that the claim language is limiting because "the purpose of sequencing the predefined subsequences is to obtain sequence tags that align ***only*** to those predefined subsequences." Brief at 19 (emphasis added); *see also id.* at 25-26. That argument is equally conclusory.[6] The claim simply does not say that—indeed, it does not use the word "only" at all. The claim recites that "sequence tags aligning to the predefined subsequences" *are* obtained, but it does not preclude obtaining other sequence tags in addition to them.

B. The Specification Does Not Support Limiting The Construction To Any Particular Sequencing Method

Not only does Stanford's proposed construction conflict with the claim language, it is also at odds with the unambiguous disclosure of the specification, which includes detailed explanations of the random sequencing approach. As the Board correctly found (JA000011), "the Specification does not disclose sequencing ***only*** the defined sequences as [Stanford] would have us construe this phrase, but instead, it discloses sequencing the predefined sequences along with other sequences, and then using various techniques to locate the predefined sequences in the material that has been sequenced." (emphasis in original).

[6] Stanford also contends that the claim language limits sequencing to ***only*** the predefined subsequences because the sequencing results in "sequence tags aligning to *the* predefined subsequences." *See* Brief at 25-26; *see also id.* at 29-30 (making similar argument regarding the use of the term "subsequences" in steps (c) and (d) of claim 1). This argument is likewise flawed. At a minimum, the comprising language of the claim does not preclude obtaining sequence tags that align to sequences in addition to *the* predefined subsequences.

1. The Specification Describes In Detail The Use Of Random Shotgun Sequencing

As mentioned above, the claim term "sequencing predefined subsequences" and the phrase "targeted sequencing" (which Stanford now seeks to merge into the claim term) are not used anywhere in the specification. While the specification does make use of related terms to describe the invention, it does so in the context of *both* shotgun sequencing and the embodiment that Stanford calls "targeted sequencing."

The term "predefined" appears twice in the specification. First, it is used in the context of "predefined sequences," in which the patent describes a "sequencing method which selectively captures sample molecules containing certain predefined sequences." JA000074 at 14:26-28. Second, it is used in the context of "predefined windows," JA000069 at 4:64-67, in which the patent describes using random shotgun sequencing to generate sequence tags aligning to a number of windows of defined length created along the chromosome, such that the windows cover each chromosome in question, except for non-informative regions, *id.* at 4:56-5:9; *see also* JA000010-11.

The term "subsequences" is used in only one portion of the specification. JA000074 at 13:65. In this disclosure, the specification describes what methodologies "may" be employed for "sequencing selected subsequences." *Id.* One approach involves sequencing that "selectively ignores certain sequence

information by using a sequencing method which selectively captures sample molecules containing certain predefined sequences." *Id.* at 14:24-28. This section of the specification also explains that, when "subsequencing," "[o]ne may also use the sequencing steps exactly as exemplified," *id.* at 14:28-29, and the examples all describe sequencing "with high throughput shotgun sequencing technology," JA000077 at 20:30-32. Furthermore, the same section of the specification explains that "[o]therwise, the method proceeds as described below . . . ," JA000074 at 14:33, following which is a disclosure entitled "Shotgun Sequencing of Cell-Free Plasma DNA," *id.* at 14:56.

Stanford's contention (at 33-34) that the specification uses the terms "predefined sequences" and "subsequences" only to describe targeted sequencing is simply wrong.

2. The Construction Must Cover The Preferred Random Sequencing Embodiments

Stanford contends (at 27-28) that because the '076 Patent claims need not cover every embodiment disclosed in the patent, the Court should limit the claims to exclude all of the random or shotgun sequencing embodiments. That is not the law.[7]

[7] Stanford's further contention that the specification's disclosure of shotgun sequencing embodiments "concerns a separate invention that is the subject of a separate patent (U.S. Patent No. 8,195,415)" is unsupported by any evidence in the record, and on that basis alone should be disregarded. *See* Brief at 27-28.

While a patent's claims need not cover every disclosed embodiment, it is settled law that "a claim construction that excludes a preferred embodiment . . . is rarely, if ever correct and would require highly persuasive evidentiary support." *EPOS Techs. Ltd. v. Pegasus Techs. Ltd.*, 766 F.3d 1338, 1347 (Fed. Cir. 2014) (internal quotation marks and citations omitted). As the Board correctly found, Stanford's proposal to limit claim 1 to what it calls "targeted sequencing" would improperly exclude both the preferred embodiment and the only examples provided in the patent. *See* JA000011-12. Indeed, the section titled "Detailed Description of the Preferred Embodiment," *see* JA000071 at 8:31-32, is replete with descriptions of "shotgun sequencing," including disclosure of "mapping shotgun sequence information," *e.g.,* JA000074 at 11:46-54, describing the utility of "shotgun sequencing" in the invention, JA000074 at 13:3-10, and an entire subsection detailing the mechanics of "Shotgun Sequencing of Cell-Free Plasma DNA," JA000074-77 at 14:56-19:36. And every single example in the "Examples" section involves shotgun sequencing. *See* JA000077 at 20:30-32 ("The examples below describe the direct sequencing . . . with high throughput shotgun sequencing technology . . .").

Stanford has not come close to providing the "highly persuasive evidentiary support" for its contention that the claims should exclude this preferred embodiment. *See EPOS*, 766 F.3d at 1347. Stanford made no prosecution history

disclaimer of random shotgun sequencing—indeed, the issue of random versus targeted sequencing was never even raised during examination. *See, e.g., N. Am. Container, Inc. v. Plastipak Packaging, Inc.*, 415 F.3d 1335, 1346 (Fed. Cir. 2005) ("[T]he fact that claims do not cover certain embodiments disclosed in the patent is compelled when narrowing amendments are made in order to gain allowance over prior art."). Nor, as demonstrated in Argument section II.B.1 above, are the shotgun sequencing embodiments "inconsistent with unambiguous language in the patent's specification . . . ." *See, e.g., Sinorgchem Co. v. ITC*, 511 F.3d 1132, 1138 (Fed. Cir. 2007). *See also* Statement of the Case at section II.B.1. To the contrary, shotgun sequencing makes up almost all of the specification's disclosure.

Stanford's contention (at 32-33) that "targeted sequencing is explicitly disclosed as a preferred embodiment" is immaterial. It is undisputed that even if what Stanford calls "targeted sequencing" is a preferred embodiment, the specification makes clear that random shotgun sequencing is also a preferred embodiment. The Board's construction, consistent with the unmodified claim term "sequencing," does not exclude either one. Rather, it expressly "decline[d] to limit 'sequencing predefined subsequences' to any particular sequencing method, but construe[d] the term as encompassing sequencing methods such as random shotgun sequencing, as well as sequencing by hybridization." *See* JA000013. The Board was right.

3. There Is No Unambiguous Disclaimer Of Random Or Shotgun Sequencing Embodiments In The Specification

"[C]laims will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope." *E.g., Innova/Pure Water, Inc. v. Safari Water Filtration Sys.*, 381 F.3d 1111, 1117 (Fed. Cir. 2004) (internal quotation marks omitted). "Disavowal requires that the specification or prosecution history make clear that the invention does not include a particular feature, or is clearly limited to a particular form of the invention." *Hill-Rom Servs. v. Stryker Corp.*, 755 F.3d 1367, 1372 (Fed. Cir. 2014) (internal quotation marks and citations omitted).

Here, there is no clear disclaimer or restrictive lexicography. To the contrary, the specification states that "[i]t will be apparent to those skilled in the art that a number of different sequencing methods and variations can be used." JA000074 at 13:13-15. Moreover, as both the Board and district court recognized, even the passage in the specification on which Stanford relies does not exclude random sequencing.

Stanford argues (at 30-31) that the specification limits the claims because it describes a "subsequencing method" involving "selectively captur[ing]" that is (a) "an alternative method" and (b) "in one aspect contrary to conventional massively parallel sequencing methodologies . . . ." But this falls far short of the "words of manifest exclusion or restriction" required to constitute a claim scope disclaimer. *See Hill-Rom*, 755 F.3d at 1372. This passage does not even purport to

define "the invention" or "all embodiments" of the invention—on its face it describes just "one aspect." *See id.* Nor does the passage state that the invention "requires" the embodiment it describes or that it is even an "important feature." *See id.* Indeed, the specification nowhere "disparages" the shotgun sequencing methods that are purported alternatives to the disclosed embodiment. *See id.* To the contrary, the vast majority of the specification—including every example—describes the utility of shotgun sequencing in the invention.

Moreover, the patent's characterization of the selective capture embodiment as "alternative" does not categorically exclude random sequencing. The "one aspect" of this embodiment that differs from "*conventional* massively parallel sequencing methodologies" is that it "selectively ignores certain sequence information." JA000074 at 14:22, 14:25-26. This does not preclude shotgun sequencing altogether. To the contrary: "[o]therwise, the method proceeds as described below," *id.* at 14:33, which includes details of "shotgun sequencing of cell-free plasma DNA," *id.* at 14:56. In other words, even the one embodiment in the specification to which Stanford points does not exclude shotgun sequencing.

In any event, the issue here is not whether targeted sequencing differs from random sequencing. It is whether both sequencing techniques are covered by the language of the claims read in light of the disclosures of the specification. They

plainly are: the claims simply say "sequencing" and do not specify *how* to sequence.

C. The Doctrine Of Claim Differentiation Requires A Construction For Claim 1 That Is Broader Than Selective Sequencing

The Board correctly determined that the doctrine of claim differentiation precludes limiting claim 1 to just "targeted" or "selective" sequencing. JA000012. According to the doctrine, "the presence of a dependent claim that adds a particular limitation raises a presumption that the limitation in question is not found in the independent claim . . . ." *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 910 (Fed. Cir. 2004).

As the Board recognized, dependent claim 9 recites only a single limitation beyond those of claim 1 from which it depends: that "said sequencing comprises *selectively sequencing nucleic acid molecules comprising the predefined sequences.*" JA000012; JA000085 (emphasis added). The Board reasoned that the additional limitation of "*selectively* sequencing" in claim 9 further supports the conclusion that the unmodified "sequencing" limitation of claim 1 is broader. JA000012. Indeed, given that that is the only additional limitation added in claim 9, failure to differentiate its "meaning and scope" from that of claim 1 would render claim 9 "superfluous." *See Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316 (Fed. Cir. 2001).

As the Board aptly noted, "[Stanford] has not provided evidence or argument sufficient to rebut the presumption" of claim differentiation. JA000013; *see also Liebel-Flarsheim*, 358 F.3d at 910 (finding that the presumption of claim differentiation has only been overcome in limited situations where "the circumstances suggest a different explanation, or if the evidence favoring a different claim construction is strong"). Stanford now claims in this appeal (at 39) that the presumption is overcome because "the specification of the '076 patent clearly describes embodiments that involve only the selective sequencing of certain predefined subsequences." This proves nothing. There is no dispute that the specification discloses embodiments that include various types of sequencing. What is important—and what Stanford fails to acknowledge—is that the broader claim 1 covers all types of sequencing, while narrower claim 9 further limits the claim to specific sequencing embodiments. The Board correctly applied the claim differentiation doctrine.

III. Stanford Is Precluded By Law From Seeking Its Proposed Narrow Construction

A. Stanford Impermissibly Seeks A Purported "Broadest Reasonable Interpretation" That Is Narrower Than The Construction It Advocated To, and Was Adopted By, The District Court

Stanford erroneously argues (at 12) that the district court in the related litigation "agreed with Stanford that although the claims are limited to targeted sequencing, they are not limited to a single method of targeted sequencing." In

fact, the district court expressly held the opposite: "claim 1 must encompass sequencing types that would include both massively parallel sequencing *and other types of sequencing*." JA002162 (emphasis added). The district court recognized that "many of the passages that describe the invention . . . do not specify the type of sequencing that is being used." JA002161. According to the district court, "[t]he patent's abstract and its description distinguishing prior art *are not limited only to targeted sequencing*." JA002161-62 (emphasis added). In addition, the district court observed that "although the specification lists several examples of how to sequence predefined subsequences, including selective capture of molecules, this is not an exhaustive or limiting list." JA002163. Accordingly, the district court construed the term as "sequencing predetermined polymorphism-independent subsequences of maternal and fetal chromosomes"—which, on its face, lacks any limitation to a particular type of sequencing. JA002163.

Now, in an attempt to circumvent the asserted prior art, Stanford seeks a "broadest reasonable interpretation" that would be *even narrower* than the district court's *Phillips* construction. This violates the most basic principles of claim construction. *See, e.g., Facebook, Inc. v. Pragmatus AV, LLC*, 582 Fed. Appx. 864, 869 (Fed. Cir. 2014) (non-precedential opinion) ("The broadest reasonable interpretation of a claim term may be the same as or broader than the construction

of a term under the *Phillips* standard. But it cannot be narrower. Thus, the Board's [narrower] construction cannot be the broadest reasonable one.").

B. Stanford Is Judicially Estopped From Seeking Its Limited Construction Because It Directly Contradicts Stanford's Successful Arguments In The District Court

In addition to being impermissibly narrow, Stanford's proposed claim construction flatly contradicts the arguments it successfully made before the district court in the related litigation. Stanford's about-face is equitably barred. Under the doctrine of judicial estoppel, "where a party *successfully* urges a particular position in a legal proceeding, it is estopped from taking a contrary position in a subsequent proceeding where its interests have changed." *RF Delaware, Inc. v. Pac. Keystone Techs., Inc.*, 326 F.3d 1255, 1262 (Fed. Cir. 2003) (emphasis in original); *see also Organic Seed Growers & Trade Ass'n v. Monsanto Co.*, 718 F.3d 1350, 1358-59 (Fed. Cir. 2013).

Before the district court, Stanford proposed a construction for "*sequencing predefined subsequences* of the maternal and fetal DNA" that read "*sequencing predetermined polymorphism independent subsequences* of pregnant human female and fetal chromosomes." JA002161. The district court adopted Stanford's proposed construction of the relevant part of this term verbatim. JA002163. (The only change the district court made to Stanford's construction was to substitute "maternal" for "pregnant human female" in a portion of the term that is not at issue

here.) This construction does not exclude random sequencing or otherwise characterize the *type* of sequencing to be done.

Importantly, Stanford successfully persuaded the district court *not* to limit the claims to the embodiment at column 14, lines 22-28 of the specification, arguing that "[t]he Federal Circuit has cautioned against limiting a claim to particular embodiments unless the patentee has demonstrated a 'clear intention' through 'words or expressions of manifest exclusion or restriction' to limit the claim's scope . . . Here, the patentee has evinced no such intent." JA004529. And at the *Markman* hearing, Stanford reiterated its position that the disclosure at "column 14 deep in the patent," which describes "selectively ignor[ing] certain sequence information," "should not be inserted into the claim when the claim language doesn't have the limitation and there's other embodiments." JA009141 at 45:8-14. That is the very disclosure that Stanford now advocates *should* limit the claims in this appeal. *See* Brief at 30-31 (asserting that "[a] person of ordinary skill in the art would have known from these disclosures [at column 14, lines 21-27] that the '076 patent is describing targeted sequencing, and specifically contrasting it with random sequencing.").[8]

[8] Stanford also successfully persuaded the district court to limit the term to sequencing "*polymorphism independent* subsequences." JA002161 (emphasis added). However, the only sequencing technique described as being polymorphism-independent in the patent is shotgun sequencing. *See* JA000069 at 4:19-25 ("Exemplified below is the successful use of shotgun sequencing . . . This

Stanford's attempt to flip-flop is inequitable. *See, e.g., Transclean Corp. v. Jiffy Lube Int'l, Inc.*, 474 F.3d 1298, 1307 (Fed. Cir. 2007) (holding that the doctrine of judicial estoppel is an "equitable doctrine" that "prohibits a party from taking inconsistent positions in the same or related litigation . . . to protect the integrity of the judicial process") (internal citations omitted). If successful here, Stanford would derive the unfair advantage of a broad *Phillips* construction for purposes of infringement in the district court, and a clearly contradictory narrow construction for purposes of avoiding prior art before the Board. This Court has long recognized that "[a] patent may not, like a 'nose of wax,' be twisted one way to avoid anticipation and another to find infringement." *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1351 (Fed. Cir. 2001). IPR proceedings under the America Invents Act ("AIA") do not change this fundamental principle of consistency.

In fact, the estoppel provisions imposed under the AIA make consistency that much more important because infringement and prior art invalidity can now be litigated in two different forums. If Ariosa were permitted to argue these same prior art-based invalidity grounds in the related district court litigation, Stanford

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forms the basis of a universal, polymorphism-independent non-invasive diagnostic test for fetal aneuploidy."); JA000077 at 20:30-39 ("The examples below describe the direct sequencing of cell-free DNA . . . with high throughput shotgun sequencing technology . . . The sequencing approach is polymorphism-independent . . ."); JA001378-79 at ¶¶ 57-58; JA001210 at ¶ 46.

would be bound by the broad construction it successfully advocated there, a construction under which the claims are clearly invalid. But the AIA's estoppel provisions prevent this. Stanford cannot be permitted to whipsaw the different forums to its maximum tactical advantage. This is not what the AIA was designed to do.

C. Ariosa's Claim Construction In The IPR Proceedings Has Been Consistent With The Broadest Reasonable Interpretation, Which Is *Broader* Than The *Phillips* Construction

Stanford argues (at 38-39) that the Board erred by not applying what amounts to an estoppel on Ariosa's unsuccessful arguments in the district court litigation. Stanford has it backwards. "[E]stoppel [does] not bar [a party] from departing from a claim construction theory unsuccessfully advocated before the trial court." *Lava Trading, Inc. v. Sonic Trading Mgmt., LLC*, 445 F.3d 1348, 1353 (Fed. Cir. 2006). In any event, there is nothing improper about advocating for a *broader* "broadest reasonable interpretation" in IPR proceedings as compared to district court litigation. *See, e.g., Facebook,* 582 Fed. App'x. at 869 (non-precedential opinion) ("The broadest reasonable interpretation of a claim term may be the same as or broader than the construction of a term under the *Phillips*

standard."). Ariosa's arguments in district court do not impact the correct claim construction in this IPR.[9]

IV. The Board's Findings That The '076 Claims Are Invalid Over Lo Are Correct Under Either Interpretation Of "Sequencing Predefined Subsequences"

Stanford's only challenge to the Board's findings on invalidity (at 40-46) is that *if* the Board had adopted Stanford's narrow proposed construction, the Lo reference allegedly would not anticipate the claims or render them obvious because Lo purportedly does not teach "targeted sequencing." *Id.* at 40-46. This argument fails to address the substantial evidence cited by the Board to support its finding that *even under Stanford's erroneous claim construction* the Lo reference still teaches the purported "targeted" or "selective" sequencing embodiment of the challenged claims, and therefore alone or in combination with Brennan or Li, it renders all of them invalid. This finding of fact is entitled to deference. *See, e.g.*, *Shimano*, F. App'x. at 1006 ("What a prior art reference discloses is a question of fact as to which the Board's findings are entitled to deference under the

[9] Moreover, Ariosa expressly argued in the district court that claim 1 covers sequencing that "can include sequences other than the predefined subsequences." *See, e.g.,* JA003425. Notwithstanding, to the extent that the Court considers Ariosa's arguments in the district court, it should do so only in a context that includes Stanford's contrary arguments there. As between Ariosa and Stanford, it is Stanford that must be bound by events in the district court because it is Stanford that prevailed there and it did so on a broader construction.

'substantial evidence' standard.") (quoting *In re ICON Health & Fitness*, 496 F.3d at 1378).

The Board found that based on a plain reading, the Lo reference, particularly at paragraph 72, teaches a "pre-selection step" as Stanford contends is recited by the '076 Patent claims. *See, e.g.*, JA000020-21; JA000023-27. The passage states, in pertinent part:

> In another embodiment, the fraction of the nucleic acid pool that is sequenced in a run is *further sub-selected prior to sequencing*. For example, *hybridization based techniques* such as *oligonucleotide array* could be used to *first sub-select for nucleic acid sequences* from certain chromosomes, e.g. a potentially aneuploid chromosome and other chromosome(s) not involved in the aneuploidy tested. Another example is that a certain sub-population of nucleic acid sequences from the sample pool is *sub-selected or enriched prior to sequencing*. . . . In one embodiment, a portion or subset of the pre-selected pool of nucleic acids is sequenced randomly.

JA001015 at ¶ 72 (emphasis added).[10] It is clear on the face of paragraph 72 that there is a "pre-selection" step, at a minimum, because it teaches sequencing nucleic acids that are "sub-selected prior to sequencing." *See id.* This language is unambiguous. Thus, even if a "preselection" step were required for "sequencing

[10] Indeed, the plain language in Lo paragraph 72 mirrors the column 13-14 disclosure of the '076 Patent that Stanford claims supports its limiting construction. *See* JA000074 at 13:65-55 ("In sequencing *selected subsequences*, one may employ sequence-based methodologies such as *sequencing by array* . . .") (emphasis added); *id.* at 14:8-10 ("The sample is rendered single stranded and *captured under hybridizing conditions* . . .") (emphasis added); *id.* at 14:25-28 ("This alternative method selectively ignores certain sequence information by using a sequencing method which *selectively captures* sample molecules containing certain pre-defined sequences.") (emphasis added).

predefined subsequences" as Stanford now contends, the plain language of this disclosure teaches it. And the Board found that persons skilled in the art would understand the disclosure that way. *See* JA000026 (citing JA003061 at ¶ 15). Crediting Dr. Morton's testimony, for example, the Board found that "when a potential aneuploid chromosome and a reference chromosome are preselected using a DNA array," as taught in Lo paragraph 72, "only those fragments that hybridize to the array are sequenced and aligned with chromosomal sequences . . . ." *Id.*[11]

Based on this substantial evidence, the Board concluded that the Lo disclosure at paragraph 72 is expressly covered by the '076 Patent's selective

[11] Contrary to Stanford's contentions (at 47-49), the Board exercised proper discretion in considering paragraph 15 of the Second Morton Declaration. *See, e.g., Shu-Hui Chen v. Bouchard*, 347 F.3d 1299, 1307 (Fed. Cir. 2003) (reviewing evidentiary rulings for abuse of discretion). Paragraph 15 explains how a person skilled in the art would understand Lo paragraph 72. *See* JA003061 at ¶ 15; JA000026; JA000036. The Board properly rejected Stanford's motion to exclude the paragraph because Stanford's objection to it—"that the figure at the end of the paragraph contains an error"—"go[es] more to the weight that paragraph . . . should be afforded, rather than to its admissibility." JA000036. Stanford's new claim (at 48-49) that Dr. Morton used the second declaration to change her testimony is wrong, and in any event irrelevant, because any change in testimony also would go to the weight of the evidence, not its admissibility. *See, e.g.*, *i4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 852 (Fed. Cir. 2010) ("[D]isputes about the degree of relevance or accuracy . . . may go to the testimony's weight, but not its admissibility."). Stanford's further claim (at 49) that it could not respond to the declaration is also inaccurate. Stanford deposed Dr. Morton for an entire day and submitted fifteen pages of Observations in response to the declaration. JA003144-3363; JA000432-48. And Stanford's own expert, Dr. Detter, dedicated four pages of his declaration to discussing Lo paragraph 72. *See* JA003667-70 at ¶¶ 64-69.

sequencing embodiment. *See id.* In order for this Court to overturn the Board's factual finding in this regard, the Court would have to find that no reasonable mind would accept the Board's evidence as adequate to support its conclusion. *See, e.g., Consol. Edison*, 305 U.S. at 229 (holding that "substantial evidence" is "such relevant evidence as a reasonable mind might accept as adequate to support a conclusion"); *see also M.Z. Berger & Co. v. Swatch AG*, 787 F.3d 1368 (Fed. Cir. 2015) (same). There is no basis for the Court to reach such a conclusion, particularly given the plain language of Lo paragraph 72 on its face and the expert testimony confirming that persons skilled in the art would understand it in accordance with its plain meaning. That Stanford or its expert prefer to draw a different conclusion from the evidence "does not prevent [the Board's] finding from being supported by substantial evidence." *See In re Applied Materials*, 692 F.3d at 1294. And the Board's "decision to favor" its conclusion over that of Stanford "must be sustained by this court as supported by substantial evidence." *See In re Bayer Aktiengesellschaft*, 488 F.3d at 970.

Stanford's arguments simply fail to acknowledge this standard. Rather, Stanford's entire argument erroneously rests on disagreements with how the Board interpreted the Lo reference. First, Stanford contends that the Board erred because it ignored Dr. Morton's testimony (taken out of context) that "Lo does not teach *how* to preselect the molecules that are going to be sequenced . . ." Brief at 40-42

(emphasis added). The Board did not ignore this testimony, it simply found it immaterial. As the Board recognized, "neither the language of the claim, nor the remainder of the Specification, defines *how* the subsequence is predefined or predetermined." JA000024 (emphasis added). And Stanford confirmed this very point in its oral argument at the district court *Markman* hearing, urging that "the specification does not impose any limitation regarding how the sequences are selected." JA004227-28 at 44:25-45:1.

Second, Stanford claims (at 43-46) that the Board erred in rejecting its argument that Lo teaches a different kind of targeted sequencing than the '076 Patent. According to Stanford, unlike the preselection allegedly recited in the '076 Patent claims, Lo only teaches preselecting "entire chromosomes" or "all of the fragments associated with a chromosome for sequencing." *Id.* But the Board rightly disregarded Stanford's arguments on this issue because there is simply no support for them.

The pertinent language of Lo paragraph 72 refers only to selecting "sequences from certain chromosomes." JA001015 at ¶ 72. There is no qualifier to this phrase. The Lo disclosure does *not* specify *all* "sequences from certain chromosomes," nor does it limit itself to the *entirety* of "certain chromosomes," as Stanford would have it (at 43-44). Based on its plain English reading, "sequences

from certain chromosomes" could refer to some or all of such sequences. Stanford's attempt to distinguish Lo in this regard is utterly without foundation.

Even if Stanford's reading of Lo paragraph 72 were correct (it is not), the Board still properly found that Stanford provides no comprehensible support for its contention that "using an array to select all fragments associated with an entire chromosome[] is not the same concept as predefining subsequences for sequencing as required by the claims of the Fan '076 patent." *See* JA000024. The Board accurately reasoned that "two or more subsequences can encompass the entire length of the chromosome." JA000024-25. And the Board therefore held that "although Lo may in fact be using the oligonucleotide array to sub-select for sequences along the entire length of a desired chromosome, the oligonucleotides that make up the array are selecting for subsequences of the chromosome, which subsequences may then be analyzed using massively parallel sequencing." JA000025.

Third, Stanford claims that Lo discloses only a single selective sequencing embodiment that combines array-based pre-selection with random sequencing. Brief at 45-46. According to Stanford, the Board erred in refusing to address Stanford's scientific theories under which this purported single embodiment falls outside the scope of the '076 Patent claims. *Id.* But the Board had no need to reach those scientific theories because Lo's disclosure is not in fact so limited.

As the Board recognized, the Lo disclosure of pre-selection is not restricted to array-based methods. Rather, the disclosure provides that "*[f]or example*, hybridization based techniques such as oligonucleotide array could be used to first sub-select for nucleic acid sequences from certain chromosomes . . ." JA001015 at ¶ 72 (emphasis added); *see also* JA001016 at ¶ 79 (further teaching that "sequences originating from a potentially aneuploid chromosome and one or more chromosomes not involved in the aneuploidy *could be* enriched by hybridization techniques *for example* onto oligonucleotide microarrays." (emphasis added)). Lo also teaches other methods for how "the fraction of the nucleic acid pool that is sequenced in a run is sub-selected prior to sequencing," including "[f]or example . . . one may use one or more methods known to those of skill in the art to fractionate the nucleic acid sequences in the sample according to molecule size, e.g., by gel electrophoresis or size exclusion columns or by microfluidics-based approach." JA001015 at ¶ 72.

The Board also observed that the Lo disclosure is not limited to "random" sequencing. The Board found that "[t]he ordinary artisan would understand that the sub-selection described by paragraph 72 of Lo could be performed before performing any of the sequencing methods disclosed by Lo, including massively parallel sequencing." JA000027. Indeed, paragraph 72 of Lo teaches only that

"*[i]n one embodiment*, a portion or subset of the pre-selected pool of nucleic acids is sequenced randomly." *Id.* (emphasis added).

Last, Stanford argues (at 46-47) that the Board erred in finding that the Lo reference anticipates the '076 Patent claims because "the Background section of Lo disparages methods that only analyze sequences 'selected prior to nucleic acid analysis' . . . ." This argument is both incorrect and immaterial. This Court has held that "even if the reference discloses the [embodiment] within the context of a reference that 'disparages' or 'teaches away,' we do not consider those issues in the context of an anticipation analysis." *Allergan, Inc. v. Apotex, Inc.*, 754 F.3d 952, 959 (Fed. Cir. 2014); *see also Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1378 (Fed. Cir. 2001) ("[T]he question whether a reference 'teaches away' from the invention is inapplicable to an anticipation analysis.").

Moreover, Stanford's only "support" for its "disparaging" language argument is its expert's conclusory opinion that Lo "disparages" so-called targeted sequencing "as providing too few data points for accurate analysis in maternal samples." Brief at 46-47. But the language of Lo does not say that; rather, Lo merely explains that in certain prior art digital PCR techniques the targeted loci and associated primers are selected ahead of time. JA001010-11 at ¶ 10. Stanford and its expert are extrapolating with no basis. The Board properly disregarded this unsupported argument. *See Rohm & Haas Co. v. Brotech Corp.*, 127 F.3d 1089,

1092 (Fed. Cir. 1997) ("[N]othing in the rules or in our jurisprudence requires the fact finder to credit the unsupported assertions of an expert witness.").

V. The Board's Evidentiary Decisions Were Proper And Should Not Be Disturbed

A. The Board Supported Its Construction With Sufficient Evidence

As demonstrated above, the evidence overwhelmingly supports the Board's broadest reasonable interpretation of "sequencing predefined subsequences" as not limited to any particular sequencing technique. Stanford's assertion (at, e.g., 37) that "the [Board] cited no evidence for [its] interpretation" is plainly erroneous. The Board expressly cites to at least the following evidence in its Decision:

- the fact that "the term 'targeted sequencing' nowhere appears in the Specification of the '076 patent," JA000010;
- the "context of the claim as a whole in light of the teachings of the specification," including the claims' recitation of obtaining "sequence tags," which the specification discusses only "in the context of random shotgun sequencing," *id.*;
- the disclosure in the Specification of "the use of a large number of windows of defined length created along the chromosome . . . [wherein] values[] are calculated for different windows and compared," based on "sequence tags within a series of *predefined windows* of equal lengths along different chromosomes . . . ," JA000011 (emphasis in original);
- the fact that "the '076 patent also provides examples that describe 'direct sequencing of cell-free DNA from plasma of pregnant women with high throughput shotgun sequencing technology,'" *id.* (quoting JA000077 at 20:30-36);
- the fact that the Board's interpretation "encompasses the preferred embodiment of the '076 patent, whereas [Stanford's] proffered

construction limiting the method of claim 1 to 'targeted' sequencing, as [Stanford] defines that term, would not," JA000012;

- the doctrine of claim differentiation, noting that Stanford's proposed claim 1 limitation "that the sequencing step is limited to sequencing only the predefined sequences" already appears in dependent claim 9, JA000012-13;

- the district court's claim construction, in which "claim 1 is *not limited to* selectively capturing sample molecules, that is, *molecular preselection*." JA000013 (emphasis added).

Stanford's further assertion (at 23) that the Board erred by "support[ing] its construction with reference to a separate disclosure of 'predefined windows' that was not advocated or supported by evidence introduced by either party" is nonsensical. Nothing prevents the Board from relying on any part of the intrinsic record in its claim construction, regardless of whether one of the parties cited to it in its briefing. *See, e.g., Powell v. Home Depot U.S.A., Inc.*, 663 F.3d 1221, 1230-31 (Fed. Cir. 2011) (holding it is proper to rely on portions of a patent in claim construction even if those portions were not advocated in the proceeding below).

B. The Board Acted Within Its Discretion In Considering The Expert Testimony For Claim Construction

In the IPR, both parties supported their claim construction positions with expert testimony. The testimony of Stanford's expert, Dr. Christopher Detter, was at odds with the construction mandated by the intrinsic evidence and therefore not credible. JA000009-10. The testimony of Ariosa's experts, Drs. Cynthia Morton and Robert Nussbaum, supported the Board's interpretation. JA001206-07 at ¶ 40;

JA001209-11 at ¶¶ 45-48; JA001214-15 at ¶¶ 54-55; JA001375-82 at ¶¶ 51-65. The Board acted within its discretion in rejecting Dr. Detter's opinions and finding in accordance with Drs. Morton and Nussbaum's opinions on claim construction. Stanford's arguments (at 17, 23, 34-37) that the Board erred because (1) its decision purportedly "does not address . . . Dr. Detter's testimony that the claims do not encompass random sequencing," and (2) the Board purportedly disregarded testimony by Ariosa's experts that Stanford claims confirm its proposed construction, are factually and legally without merit.

As to Stanford's expert, the Board expressly acknowledged that "[r]elying on the Declaration of Dr. J. Chris Detter, [Stanford] asserts that 'a person of ordinary skill in the art would understand that the term 'predefined' refers to preselecting the nucleic acids to be sequenced prior to sequencing them.'" JA000009. The Board exercised its discretion in rejecting this expert witness evidence, stating that "[w]e have considered [Stanford's] contentions carefully, as well as the evidence cited by [Stanford], and we decline to adopt its proffered construction." JA000010. The Board acted well within its discretion. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1318 (Fed. Cir. 2005) (en banc) ("[A] [tribunal] should discount any expert testimony that is clearly at odds with the claim construction mandated by the claims themselves, the written description, and the

prosecution history, in other words, with the written record of the patent.") (internal quotation marks omitted).

On the other hand, Stanford contends (at 35-36) that the Board erred because it was not persuaded by purportedly damaging admissions by Ariosa's experts that Stanford claims support its construction. Stanford is wrong. Stanford falsely suggests that Dr. Morton supported its position by testifying "that the claimed method is a 'directed sequencing method,' and that 'directed sequencing is not random.'" Brief at 35 (quoting JA001917, at 21:22; JA001922, at 21:20-24). What Dr. Morton actually said is that "*part of* the method is a directed sequencing method, but it does employ what we consider very massively parallel sequencing after the sequences are selected." JA001917 at 21:20-24. More importantly, Dr. Morton explained her reading of the claims in surrounding testimony: "you're looking for particular sequences that you've selected, but the method of sequencing itself is going to sequence all of the information that you have in that sample that—that contains your selected sequences." JA001920 at 24:18-23. This can be accomplished with random sequencing. *See* Statement of the Case section I.C.1 above.[12]

[12] Stanford's reference to Dr. Morton's alleged testimony "that the '076 patent claims do not claim 'sequencing all sequences in terms of sequencing the entire human genome'" is also misplaced. *See* Brief at 35. A review of that testimony makes clear that Dr. Morton was simply emphasizing that there is a distinction between "a complete genome in a cell" and "the fragmented genome in

Stanford's arguments regarding Dr. Nussbaum are likewise inaccurate. Stanford contends that "Dr. Nussbaum . . . agrees that step (b) involves a physical pre-selection" based on his testimony that "predefined subsequences . . . refers to a physical molecule subject to a sequencing operation." Brief at 36. But Dr. Nussbaum said nothing about any form of *selection*. *See id.* Dr. Nussbaum is simply making the obvious observation that what is being sequenced must be a physical molecule. *See also* JA001376 ("the element 'predefined subsequence' in the claims . . . is itself subjected to sequencing and thus must be a nucleic acid . . . .").

In any event, all this evidence was before the Board, and the Board chose to credit certain evidence. This decision is entitled to deference. *Teva*, 135 S. Ct. at 841; *see also Bieber v. Dep't of Army*, 287 F.3d 1358, 1364 (Fed. Cir. 2002) (holding that an administrative judge's credibility-based fact finding is "virtually unreviewable on appeal").

VI. The Board Properly Considered And Rejected Stanford's Arguments Regarding Anticipation Of Claim 9

Claim 9 further limits claim 1 to "wherein said sequencing comprises *selectively sequencing* nucleic acid molecules comprising the predefined sequences." JA000085 at 36:8-11 (emphasis added). In its Decision, the Board

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the cell-free DNA." *See, e.g.,* JA001977 at 81:11-13. This has nothing to do with sequencing techniques.

found claim 9 anticipated for the same reasons it generally found that Lo paragraph 72 met the limitation of claim 1 even under Stanford's narrow interpretation. *See* JA000026-27. Given the plain language of the one additional limitation in claim 9—"selectively sequencing"—and the extensive discussion of the Lo paragraph 72 disclosure describing "selectively sequencing" in the Board's Decision on anticipation of claim 1, the Board's "path may reasonably be discerned," and should be affirmed. *See, e.g., In re Applied Materials,* 692 F.3d at 1294; *Bowman Transp., Inc. v. Arkansas-Best Freight Sys., Inc.*, 419 U.S. 281, 285-86 (1974); *e.g.,* JA000021 ("Moreover, to the extent that the claim encompasses *preselecting sequences*, Lo teaches that a fraction of the nucleic acid pool may be further *sub-selected prior to sequencing*.") (emphasis added); *see also* JA000023-26.

Stanford nevertheless contends (at 50) that the Board erred because it failed to consider Stanford's "separate argument" regarding claim 9. Stanford claims that it presented a "separate argument" because it told the Board "that '[i]f for some reason you decide that claim 1 wasn't limited as we described, claim 9 certainly is limited in that same way." *Id.* And Stanford contends that the Board erred because it ignored this purportedly separate argument. Stanford's argument makes no sense because, by Stanford's own admission, its argument as to claim 9 was the same as

its argument as to claim 1—that Lo does not anticipate under Stanford's claim construction.

The decision makes clear that the Board found claim 9 anticipated for the same reason that claim 1 was anticipated under Stanford's proposed interpretation of the phrase "sequencing predefined subsequences." *See* JA000021, JA000023-25, 27. Because the Board found claim 1 to be anticipated by Lo even if it is somehow limited to selective (or targeted) sequencing, claim 9—which is expressly limited to selective sequencing—is likewise anticipated by Lo for the same reasons: Lo discloses selective sequencing.

VII. The Board Properly Found Claims 6 And 10-11 Obvious

Stanford contends (at 51-52) that the Board erred in finding claims 6 and 10-11 obvious. Stanford's only argument is that the Board allegedly erred in finding that Lo anticipates claim 1 from which claims 6 and 10-11 depend. *Id*. In other words, Stanford offers no independent basis for the validity of these dependent claims. Because, as explained above, the Board properly found that Lo anticipates claim 1, it also properly found that claims 6 and 10-11 are obvious.

CONCLUSION

For the foregoing reasons, the Board's findings were correct, were based on substantial evidence, and should be affirmed.

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Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B) because this brief contains 13,999 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

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Dated: August 20, 2015

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CERTIFICATE OF SERVICE

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